REMARKS

Claims 1-20 are pending in the present application, of which claims 14-20 are withdrawn. With the instant amendments, claims 1, 8 and 10 are amended, claims 13-20 are canceled without prejudice, and new claims 21-23 are added. Upon entry of these amendments, claims 1-12 and 21-23 will be pending and under consideration.

I. AMENDMENTS TO THE CLAIMS

Claim 1 has been amended to recite in part "comprising orally administering to the subject about 0.1 mg to about 1.0 mg 4-methylpyrazole (4-MP) per kilogram of the subject's body mass."

Claims 8 and 10 have been amended to recite in part "wherein about 0.1 mg to about 1.0 mg 4-MP per kilogram of the subject's body mass is administered."

Support for the amendments to claims 1, 8 and 10 may be found in the specification, for example, at paragraph [0046] of the application as filed, which discloses the following:

> In certain embodiments, the amount of 4-MP administered can be between about 0.1 mg/kg to about 4 mg/kg .... In some embodiments, about 0.1 mg/kg, about 0.5 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, or about 4 mg/kg of 4-MP are administered to the subject having reduced or absent ALDH2 activity. In certain embodiments, the amount of 4-MP administered can be in the range between 0.1 mg/kg to 3 mg/kg, in the range between 0.5 mg/kg to 2 mg/kg, or in the range between 2 mg/kg to 4 mg/kg.

Applicants submit that the above disclosure provides written description support for the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP. *See* MPEP § 2163.05 (III); *In re Wertheim*, 191 U.S.P.Q. 90, 98 (CCPA 1976) (finding that a range in the specification of "25%-60%" and specific examples of "36%" and "50%" supported a limitation to "between 35% and 60%.").

New claims 21-23 are fully supported by the specification. Support for new claims 21 and 22 may be found in the specification, for example, at paragraph [0046] of the application as filed. Support for new claim 23 may be found in the specification, for example, at paragraphs [0009] and [0045] of the application as filed.

Applicants submit that the amendments to the claims are fully supported by the specification as originally filed and present no new matter. Entry thereof is respectfully requested.

II. RESTRICTION/ELECTION REQUIREMENT

The Patent Office requires Applicants to affirm the provisional election made telephonically on December 10, 2008 to prosecute with traverse the invention of Group I (claims 1-13). *See* Office Action, page 5.

Applicants hereby affirm the election, without traverse, of Group I (claims 1-13) drawn to methods of preventing or ameliorating a symptom.

III. CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 1, 3-5 and 7-13 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Japanese Unexamined Patent Application S57-106620(5) ("the '620 application"), "as evidenced by" Jacobsen *et al.*, *Alcoholism: Clinical and Experimental Research*, Vol. 20, pp. 804-809 ("Jacobsen *et al.*"). *See* Office Action, at page 6, third paragraph. Since claim 13 is canceled in the instant amendments, the rejection of this claim is moot and should be withdrawn. Applicants respectfully traverse the rejection with regard to claims 1, 3-5 and 7-12.

To establish anticipation under 35 U.S.C. § 102, the Patent Office must establish that each and every limitation of the claim is disclosed in the cited reference, either expressly or inherently. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "For a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." *See In re Bond*, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir., 1990). Thus, a cited reference must describe each and every claim limitation in order to anticipate the invention as claimed.

Neither the '620 application nor Jacobsen *et al.* teach or suggest the use of 4-MP doses within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP for preventing, reducing or ameliorating a symptom of acetaldehyde accumulation, or ethanol intolerance, in ALDH2 deficient subjects, as recited in amended claims 1, 8 or 10.

The '620 application purports to disclose oral administration of 250 mg of 4-MP hydrochloride to alcohol intolerant persons (three adult males, 55 kg to 60 kg). *See* the '620 application, at page 119 (Example of embodiment 1). According to the Patent Office, "this calculates out to a oral dose 4.17 - 4.55 mg/kg of 4-MP hydrochloride." *See* Office Action at page 12, second paragraph. The '620 application further purports to disclose doses of "100 to 500 mg (1.5 to 10 mg/kg) in terms of 4-alkylpyrazole" made into tablets or into a water-soluble salt and then administered as an aqueous solution to the alcohol intolerant persons. *See* the '620 application, at page 118, first column, fifth paragraph.

Jacobsen *et al.* purports to disclose doses of 10 to 20 mg/kg of 4-MP administered orally, and doses of 5 mg/kg of 4-MP administered intravenously, to "healthy male volunteers,"[1] presumably not alcohol intolerant persons. *See* Jacobsen *et al.* at pages 804-805 (Methods: Subjects & Study Design).

Therefore, neither the '620 application nor Jacobsen *et al.* teach or suggest the methods recited in amended claims 1, 8 or 10, wherein about 0.1 mg to about 1.0 mg 4-MP per kilogram of the subject's body mass is administered to an ALDH2 deficient subject. Because neither the '620 application nor Jacobsen *et al.* teach or suggest each and every element of amended claims 1, 8 or 10, these claims, and claims 3-5, 7, 9, 11 and 12 which depend therefrom, are novel over the '620 application and over Jacobsen *et al.*

Accordingly, Applicants respectfully request that the rejection of 1, 3-5 and 7-12 under 35 U.S.C. § 102(b) as allegedly anticipated by Japanese Unexamined Patent Application S57-106620(5) ("the '620 application"), and "as evidenced by" Jacobsen *et al.*, *Alcoholism: Clinical and Experimental Research*, Vol. 20, pp. 804-809 ("Jacobsen *et al.*"), be withdrawn.

IV. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1, 2 and 6 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Japanese Unexamined Patent Application S57-106620(5) ("the '620 application") in view of

[1] The subjects displayed no evidence of acute or chronic disease, and all had normal values from the various tests. *See* Jacobsen *et al.* at page 804 (Methods: Subjects).

Casavant, *Pediatrics*, Vol. 107, No. 1, January 2001, pp. 170 ("Casavant"). *See* Office Action at page 13.

A. The legal standard for obviousness

The Supreme Court has addressed the test for obviousness under 35 U.S.C. § 103(a). *KSR International Co. v. Teleflex Inc.,* 127 S.Ct. 1727 (2007). In *KSR*, the Supreme Court noted that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in a way the claimed new invention does." *KSR*, 127 S.Ct. at 1741. The prior art reference (or references when combined) need not teach or suggest all the claim limitations, however, Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. MPEP § 2141 III at page 2100-118 (Eighth Edition, Rev. 6, September 2007).

Turning to the instant case, Applicants respectfully traverse the rejection and submit that claims 1, 2 and 6 are not obvious over the '620 application in view of Casavant, because the references, either alone or in combination, do not teach or suggest doses within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP to treat ALDH2 deficient subjects, nor do they provide a reason why one of ordinary skill in the art would use such relatively low doses to treat ALDH2 deficient subjects.

B. The Claims are not obvious over the '620 application in view of Casavant

The instant application discloses that relatively low doses, that is, doses within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP, can increase the comfort level of ALDH2 deficient subjects when drinking alcohol.

The '620 application purports to disclose doses of "100 to 500 mg (1.5 to 10 mg/kg) in terms of 4-alkylpyrazole" to alcohol-intolerant adult males (*see* the '620 application, at page 118, first column, fifth paragraph), but does not teach or suggest doses within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP to treat ALDH2 deficient subjects, as recited in amended claim 1.

Further, Applicants respectfully submit that none of the references cited in the Office Action provide a reason for one of ordinary skill in the art to use such relatively low doses to treat ALDH2 deficient subjects, as explained below.

The art cited in the Office Action discloses that a therapeutic dose range of 10 to 20 mg/kg 4-MP will inhibit alcohol dehydrogenase activity in humans *in vivo*. *See* Jacobsen *et al.*, abstract at page 804, lines 8-11 ("4-MP in the presumed therapeutic dose range of 10 to 20 mg/kg ... inhibit[s] alcohol dehydrogenase activity in humans in vivo.") *See also* Casavant, at page 170, fourth paragraph, which describes administration of 10 to 15 mg/kg 4-MP (fomepizole) as a safe and effective blocker of alcohol dehydrogenase ("a 15 mg/kg loading dose is given intravenously over 30 minutes, followed by 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours"). Applicants submit that one of ordinary skill in the art, reading the cited art, would probably want to be within the therapeutic dose range for 4-MP, especially as this range, known to inhibit alcohol dehydrogenase activity *in vivo*, is well within toxicity limits. *See* Jacobsen *et al.*, at page 804, second column, lines 13-14 ("doses of 4-MP in the range of 10 to 20 mg/kg produce no adverse effects"). *See also* the '620 application, at page 117, second column, second paragraph, lines 5-6 ("the toxicity of 4-alkylpyrazole is generally low"). Indeed, even levels as high as 200 mg/kg appear to be well tolerated. *See* the '620 application, at page 117, second column, second paragraph, lines 19-21 ("when [4-MP was] administered orally to rats over a period of 4 weeks at a rate of 200 mg/kg per day, no anomalies were observed").

The '620 application discloses 4-MP doses which are somewhat lower than the therapeutic dose range disclosed by Jacobsen *et al.* For example, the '620 application discloses that "normally, 100 to 500 mg (1.5 to 10 mg/kg) in terms of 4-alkylpyrazole is appropriate." *See* the '620 application, at page 118, first column, fifth paragraph. Because the '620 application states that this dose range is appropriate for the intended purpose, Applicants submit that one of ordinary skill in the art would have had no reason to lower the dose of 4-MP below 1.5 mg/kg for treating ALDH2 deficient subjects. Indeed, in view of the disclosures in Jacobsen *et al.* and Casavant, Applicants submit that one of ordinary skill in the art would have been more likely to increase, not decrease, the dose of 4-MP, as a higher dose was known to be nontoxic at the time of the instant invention (*see* Jacobson *et al.*, at page 804, second column, lines 13-14), but a lower dose may not be sufficient to inhibit alcohol dehydrogenase activity *in vivo*. Accordingly, Applicants submit that based on the disclosures of the cited art, one of ordinary skill in the art would have had no reason to reduce the dose of 4-MP below 1.5 mg/kg to treat ALDH2 deficient subjects. Therefore, claim 1 and claims which depend therefrom are not obvious over the cited references.

In sum, the '620 application and Casavant, either alone or in combination, do not teach or suggest doses within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP to treat ALDH2 deficient subjects, as recited in amended claim 1. Further, none of the references cited in the Office Action, alone or in combination, provide a reason why one of ordinary skill in the art would use such relatively low doses to treat ALDH2 deficient subjects. Consequently, amended claim 1, and claims 2 and 6 which depend therefrom, are not obvious over the '620 application in view of Casavant.

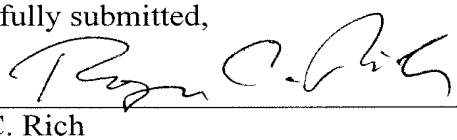
Accordingly, Applicants respectfully request that the rejection of claims 1, 2 and 6 under 35 U.S.C. § 103(a) as allegedly obvious over Japanese Unexamined Patent Application S57-106620(5) ("the '620 application") in view of Casavant, *Pediatrics*, Vol. 107, No. 1, January 2001, pp. 170 ("Casavant") be withdrawn.

CONCLUSION

No fee other than the fees for additional claims and extension of time is believed to be due in connection herewith. However, should the Commissioner determine otherwise, the Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 50-3013 (order no. 451265-999001).

Respectfully submitted,

Date: July 7, 2009



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